

REMARKS

STATUS OF THE CLAIMS

Claims 66-71 and 125-128 are pending as shown above.

REJECTIONS WITHDRAWN

The rejection under 35 U.S.C. § 112, 2nd paragraph as allegedly indefinite has been withdrawn. (Final Office Action, page 7).

35 U.S.C. § 103(a)

Claims 66-71 and 125-128 were newly rejected under 35 U.S.C. § 103(a) as allegedly obvious over Clontech in view of U.S. Patent No. 5,635,355 (hereinafter "Grosveld"). (Final Office Action, pages 2-6). While it was acknowledged that Clontech does not disclose a library where each and every polynucleotide has an insert that consist essentially of accessible regions of cellular chromatin, it was alleged that Grosveld provides the motivation to modify Clontech to clone regulatory sequences. *Id.*

In response to Applicants' arguments that Grosveld contains no suggestion as to libraries made by the claimed methods, it was asserted (Final Office Action, page 6):

...no argument is to provided as to the examiner's position that Grosveld et al. suggest such cloning and such clones because, as set forth above, they expressly claim "a method of obtaining a DNA fragment comprising a dominant activator sequence, comprising providing a candidate DNA fragment comprising a DNaseI hypersensitive site from a genetic locus" ..., and "ligating the fragment to an expressible gene to form a construct" (see claim1 therein), and such DNase I hypersensitive fragments should encompass essentially the fragments from readily available clones or from the fragments identified in column 8 and such constructs, collectively are a library, as would be readily apparent to one of ordinary skill in the art of molecular cloning.

Furthermore, in response to Applicants' arguments that Grosveld does not teach the steps of making a library as claimed, which results in different libraries, the Examiner stated (Final Office Action, page 7):

This is also unpersuasive because the method of claim 66 comprises contact[ing] the chromatin with a probe that cleaves accessible regions, then deproteinize[ing] the cleaved chromatin, and then digest[ing] with a nuclease to generate a collection of polynucleotides. The method of Grosveld et al. in fact comprises these steps as, admitted by applicant in the response on page 6, their method comprises treating the nuclei, which comprises chromatin, with DNase I, which is a nuclease, but is also a probe based on the definition and examples of "probe" in the instant application (Instant claim 125 actually claims that the probe is a nuclease), then deproteinize the cleaved chromatin, and then digest them with Asp718 or BglII to generate a collection of polynucleotides, where the Asp718 or BglII is a restriction enzyme, which is also a nuclease....

Applicants again strongly traverse the rejections and remarks, particularly the assertion that Applicants have not addressed what Grosveld teaches, or in this case, fails to teach.

It remains the case that the Clontech library is admittedly silent as to the claimed libraries. Thus, Grosveld must teach or suggest the claimed elements in order for the Examiner to establish a *prima facie* case of obviousness. This has not been, and indeed cannot be, done.

Claim 66, from which all claims directly or ultimately depend, is drawn to a library of polynucleotides in which each polynucleotide comprises an insert sequence consisting essentially of an accessible region of cellular chromatin. Moreover, the library is obtained by the specific, recited steps, including (a) contacting cellular chromatin with a probe that cleaves the chromatin at accessible regions of cellular chromatin; (b) deproteinizing the cleaved chromatin; (c) digesting the deproteinized chromatin with a nuclease to generate a collection of polynucleotide fragments; and (d) selectively cloning polynucleotide fragments comprising one end generated by probe cleavage.

As previously noted, it is axiomatic that to establish *prima facie* obviousness of a claimed invention, all of the claim features must be taught or suggested by the cited references. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Accordingly, in order to establish a *prima facie* case of obviousness, Grosveld must provide what is missing from the Clontech reference in terms of the claimed elements, namely by teaching libraries consisting essentially of inserts corresponding to accessible regions of cellular chromatin, which libraries are obtained by the recited steps.

In point of fact, there are absolutely no teachings whatsoever in Grosveld regarding libraries as claimed. The claimed libraries consist essentially of inserts corresponding to

accessible regions and are obtained by specific cloning steps. By contrast, Grosveld states that hypersensitive sites may be "mapped" (col. 7, lines 59-63). The only cloning referred to in Grosveld involves construction of a single target sequence that, in certain cells, comprises a DNase hypersensitive site. Cloning of "the target sequence" (*i.e.*, a single sequence) into a vector results in the production of multiple copies of the same sequence, or what is normally referred to in the art as a clone. It does not produce a library of polynucleotide sequences in the same way that a building containing multiple copies of the same book for loan would not be considered a library.

In regards to the Examiner's assertions that no arguments were provided as to the Examiner's position that Grosveld "suggests" cloning a library as claimed, it is reiterated that the Examiner has taken portions of Grosveld regarding cloning out of context and that this reference fails to teach cloning of fragments as claimed.

In particular, Grosveld teaches (at column 8) that, in one case, nuclei were treated with DNase I (first enzyme), then deproteinized DNA was recut with *Asp718* or *BglII* (second enzymes). *See*, Grosveld, column 8, lines 17-32. In a second case, nuclei were treated with DNase I (first enzyme), and deproteinized DNA was recut with *BamHI* (second enzyme). *See*, Grosveld, column 8, lines 34-41. However, nowhere does Grosveld suggest that these fragments are cloned to make a library. To the contrary, the portions of Grosveld from column 15 (cited by the Examiner), the DNA fragments that are cloned are an *XbaI-XbaI* fragment (containing DNaseI HS1), a *HindIII-HindIII* fragment (containing DNaseI HS2), a *Asp718-SalI* fragment rendered blunt-ended (containing DNaseI HS3) and a partial *SacI* fragment (containing DNaseI HS4). *See*, Grosveld, column 15, lines 16-31. Notably, none of these fragments which Grosveld teaches or suggests should be cloned correspond to a DNaseI-*Asp718* fragment, a DNaseI-*BglII* fragment or a DNaseI-*BamHI* fragment, as described in column 8 of Grosveld.

Thus, the portions of Grosveld cited by the Examiner do not teach the cloning of a collection of fragments that have been produced by contacting nuclei with a first enzyme, deproteinizing and contacting the deproteinized DNA with a second enzyme, as claimed.

Indeed, the Board of Patent Appeals and Interferences has previously determined that Examiner's assessment of what Grosveld teaches is in error. In particular, in the parent case (now U.S. Patent No. 7,217,509), the Board determined that Grosveld does not teach or suggest

cloning of fragments obtained by as recited. *See*, Decision on Appeal mailed December 21, 2006 in Appeal No. 2006-2851 (Application No. 09/844,501), pages 3-4, underlining in original:

Upon review of the disclosure of Grosveld, we do not find that the examiner has provided sufficient evidence to support a *prima facie* case of obviousness of the method of claim 123 [claim 1 of issue patent]. ...

Grosveld at column 8, lines 16-32, described deproteination steps and digestion with a second enzyme to generate fragments, such as BglII, consistent with steps (c) and (d) of claim 123. Then, "the exact location of the DNaseI hypersensitive site[s] of the 3' adult β -globin gene were determined using two single copy DNA probes and several restriction enzyme digests of DNaseI digested HEL nuclei. The data summarized in FIG. 2 (A-D) show that there is a single DNaseI hypersensitive site between the 2.3 kb BglII fragment and the 2.4 kb HindIII fragment...." Column 8, lines 48-51. Accordingly, Grosveld obtained fragments of the adult β -globin gene and probed these fragments to locate the DNaseI hypersensitive sites. Grosveld did not, according to claim 123, step (e), contact the DNA fragments obtained in step (d) with a population of vector molecules, wherein the vector molecule comprise a first end that is compatible with the first enzyme and a second end that is compatible with the second enzyme, under conditions favorable to ligation of compatible ends; or step (f), select polynucleotides comprising a DNA fragment ligated to a vector molecule. Grosveld, on the other hand, probed DNA fragments which were not ligated to a vector, and selected the DNA fragment of interest having the DNaseI hypersensitive site by its ability to bring to a probe.

The Board also confirmed that the fragments "cloned" at column 15 of Grosveld are not inserts as claimed. *See*, Decision on Appeal mailed December 21, 2006 in Appeal No. 2006-2851 (Application No. 09/844,501), pages 4-5, emphasis added:

In a different experiment, Grosveld incorporated the previously identified DNaseI hypersensitive sites into a vector or plasmid containing both the hypersensitive sites and the adult β -globin gene. Column 15, lines 6-47. The DNA fragments cloned in the experiment described in column 15 are not the same fragments described in column 8. In particular, the hypersensitive sites (HSS)-containing fragments cloned in col. 15 are not the DNaseI restriction enzyme fragments from col. 8. *See* col. 15, lines 45-46: PvuI-BstEII fragment with HSS 1 and 2; BstEII-ClaI fragment with HSS 3 and 4.

In contrast, appellants describe their method in the specification, pages 49-50, as follows. ...

For the reasons discussed herein, we do not find the examiner has provided sufficient evidence to support a *prima facie* case of obviousness. The rejection of claims over Grosveld is reversed.

Thus, for the reasons set forth in the Board decision regarding the parent application, Grosveld does not teach or suggest step (d) of the instant claims, namely selective cloning of fragments generated as claimed. As such, the claimed libraries are necessarily different in structure (by virtue of the inserts) from the single clones described in Grosveld.

In addition, in the parent, the Board determined that there was no combination of Grosveld and additional references, including the NEB restriction enzyme catalog, which teaches the step of selective cloning. *See*, Decision on Appeal mailed December 21, 2006 in Appeal No. 2006-2851 (Application No. 09/844,501), page 6:

With respect to the other pending obviousness rejections before us, all rejections stand or fall on the relevance of Grosveld to the pending claims. The examiner relies on the NEB catalog ...

We do not find that either NEB catalog, Li or Chung overcome the above noted deficiency of Grosveld and its failure to teach steps (e) and (f) of claim 123, and therefore the rejections for obviousness over Grosveld taken with NEB catalog, Li or Chung are reversed.

In sum, for the reasons of record and as set forth by the Board in the parent application, Grosveld does not teach libraries as claimed because this reference fails entirely to teach selective cloning of fragments (inserts) obtained as recited in the pending claims. Accordingly, a *prima facie* case of obviousness has not been and cannot be established and the rejection of these claims as allegedly obvious over the cited references should be withdrawn, and these claims should be allowed.

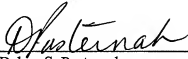
CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the claims are now in condition for allowance and request early notification to that effect.

Respectfully submitted,

Date: February 8, 2010

By: _____


Dahna S. Pasternak
Attorney for Applicant
Registration No. 41,411

ROBINS & PASTERNAK LLP
1731 Embarcadero Road, Suite 230
Palo Alto, CA 94303
Tel.: (650) 493-3400
Fax: (650) 493-3440